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CHEMICAL COMPOUNDS

The present invention relates to piperidine derivatives having pharmaceutical activity, to processes for preparing such derivatives, to pharmaceutical compositions comprising such derivatives and to the use of such derivatives as active therapeutic agents.

Pharmaceutically active piperidine derivatives are disclosed in PCT/SE01/01053, EP-A1-1013276, WO00/08013, WO01/90106, WO99/38514 and WO99/04794.

Chemokines are chemotactic cytokines that are released by a wide variety of cells to attract macrophages, T cells, eosinophils, basophils and neutrophils to sites of inflammation and also play a rôle in the maturation of cells of the immune system. Chemokines play an important rôle in immune and inflammatory responses in various diseases and disorders, including asthma and allergic diseases, as well as autoimmune pathologies such as rheumatoid arthritis and atherosclerosis. These small secreted molecules are a growing superfamily of 8-14 kDa proteins characterised by a conserved four cysteine motif. The chemokine superfamily can be divided into two main groups exhibiting characteristic structural motifs, the Cys-X-Cys (C-X-C, or α) and Cys-Cys (C-C, or β) families. These are distinguished on the basis of a single amino acid insertion between the NH-proximal pair of cysteine residues and sequence similarity.

The C-X-C chemokines include several potent chemoattractants and activators of neutrophils such as interleukin-8 (IL-8) and neutrophil-activating peptide 2 (NAP-2).

The C-C chemokines include potent chemoattractants of monocytes and lymphocytes but not neutrophils such as human monocyte chemotactic proteins 1-3 (MCP-1, MCP-2 and MCP-3), RANTES (Regulated on Activation, Normal T Expressed and Secreted), eotaxin and the macrophage inflammatory proteins 1α and 1β (MIP-1α and MIP-1β).

Studies have demonstrated that the actions of the chemokines are mediated by subfamilies of G protein-coupled receptors, among which are the receptors designated CCR1, CCR2, CCR2A, CCR2B, CCR3, CCR4, CCR5, CCR6, CCR7, CCR8, CCR9, CCR10, CXCR1, CXCR2, CXCR3 and CXCR4. These receptors represent good targets for drug development since agents which modulate these receptors would be useful in the treatment of disorders and diseases such as those mentioned above.

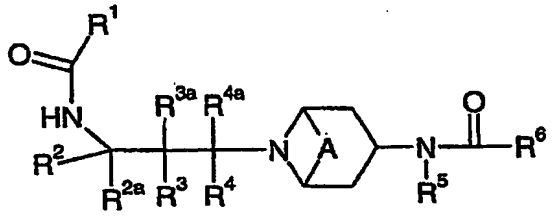
The CCR5 receptor is expressed on T-lymphocytes, monocytes, macrophages, dendritic cells, microglia and other cell types. These detect and respond to several

chemokines, principally "regulated on activation normal T-cell expressed and secreted" (RANTES), macrophage inflammatory proteins (MIP) MIP-1a and MIP-1b and monocyte chemoattractant protein-2 (MCP-2).

This results in the recruitment of cells of the immune system to sites of disease. In many diseases it is the cells expressing CCR5 which contribute, directly or indirectly, to tissue damage. Consequently, inhibiting the recruitment of these cells is beneficial in a wide range of diseases.

CCR5 is also a co-receptor for HIV-1 and other viruses, allowing these viruses to enter cells. Blocking the receptor with a CCR5 antagonist or inducing receptor internalisation with a CCR5 agonist protects cells from viral infection.

The present invention provides a compound of formula (I):



(I)

wherein:

A is CH_2CH_2 or A is absent;

R^1 is C_{3-7} cycloalkyl (substituted by one or two fluorine atoms and optionally further substituted by C_{1-4} alkyl) or N-linked heterocyclyl (substituted by one or two fluorine atoms and optionally further substituted by C_{1-4} alkyl);

R^2 is C_{3-6} alkyl or C_{3-6} cycloalkyl, or phenyl or heteroaryl either of which is optionally substituted by halogen, C_{1-4} alkyl, C_{1-4} alkoxy, $S(O)_n(C_{1-4}$ alkyl), nitro, cyano or CF_3;

R^{2a}, R^4 and R^{4a} are, independently, hydrogen or C_{1-4} alkyl;

R^3 and R^{3a} are, independently, hydrogen or C_{1-4} alkyl or C_{1-4} alkoxy;

R^5 is hydrogen, C_{1-4} alkyl (optionally substituted by halogen, hydroxy, C_{1-4} alkoxy, C_{3-7} cycloalkyl, SH, C_{1-4} alkylthio, cyano or $S(O)_q(C_{1-4}$ alkyl)), C_{3-4} alkenyl, C_{3-4} alkynyl or C_{3-7} cycloalkyl;

R^6 is phenyl, heteroaryl, phenylNH, heteroarylNH, phenyl(C_{1-2})alkyl, heteroaryl(C_{1-2})alkyl, phenyl(C_{1-2} alkyl)NH or heteroaryl(C_{1-2} alkyl)NH; wherein the phenyl and heteroaryl rings of R^6 are optionally substituted by halo, cyano, nitro, hydroxy, C_{1-4} alkyl, C_{1-4} alkoxy, $S(O)_mC_{1-4}$ alkyl, $S(O)_2NR^7R^8$, $NHS(O)_2(C_{1-4}$ alkyl), NH_2, $NH(C_{1-4}$ alkyl), $N(C_{1-4}$ alkyl)$_2$, $NHC(O)NH_2$,

$C(O)NH_2$, $C(O)NH(C_{1-4}$ alkyl), $NHC(O)(C_{1-4}$ alkyl), CO_2H, $CO_2(C_{1-4}$ alkyl), $C(O)(C_{1-4}$ alkyl), CF_3, CHF_2, CH_2F, CH_2CF_3 or OCF_3;

R^7 and R^8 are, independently, hydrogen or C_{1-4} alkyl, or together with a nitrogen or oxygen atom, may join to form a 5- or 6-membered ring which is optionally substituted with C_{1-4} alkyl, C(O)H or $C(O)(C_{1-4}$ alkyl);

m, n and q are, independently, 0, 1 or 2;

or a pharmaceutically acceptable salt thereof or a solvate thereof.

Certain compounds of the present invention can exist in different isomeric forms (such as enantiomers, diastereomers, geometric isomers or tautomers). The present invention covers all such isomers and mixtures thereof in all proportions.

Suitable salts include acid addition salts such as a hydrochloride, hydrobromide, phosphate, acetate, fumarate, maleate, tartrate, citrate, oxalate, methanesulphonate or *p*-toluenesulphonate.

The compounds of the invention may exist as solvates (such as hydrates) and the present invention covers all such solvates.

Alkyl groups and moieties preferably contain, unless otherwise specified, 1-6, especially 1-4, carbon atoms. Alkyl groups and moieties are straight or branched chain and are, for example, methyl, ethyl, n-propyl or iso-propyl.

Alkenyl includes prop-2-en-1-yl, allyl, but-3-en-1-yl, but-1-en-1-yl or 2-methylallyl. Alkynyl includes propargyl or but-3-yn-1-yl. Alkenyl and alkynyl groups and moieties are, for example, allyl or propargyl.

Cycloalkyl preferably contains, unless otherwise specified, 3-7, especially 3-6, carbon atoms. Cycloalkyl is, for example, cyclopropyl, cyclobutyl or cyclopentyl.

When A is present the central ring of formula (I) is a 3-substituted 8-aza-bicyclo[3.2.1]oct-8-yl ring. When A is absent the central ring of formula (I) is a 4-substituted piperidin-1-yl ring.

Heterocyclyl is a non-aromatic, monocyclic ring comprising at least one nitrogen, and, optionally, one further heteroatom selected from the group comprising nitrogen, oxygen and sulphur. Heterocyclyl includes aziridinyl, azetidinyl, piperidinyl, morpholinyl, thiomorpholinyl, pyrrolidinyl or piperazinyl.

Heteroaryl is an aromatic 5 or 6 membered ring comprising at least one heteroatom selected from the group comprising nitrogen, oxygen and sulphur. Heteroaryl is, for example, pyrrolyl, imidazolyl, pyrazolyl, 1,2,3-triazolyl, 1,2,4-triazolyl, oxazolyl, isoxazolyl,

oxadiazolyl, thiazolyl, isothiazolyl, thiadiazolyl, pyridinyl, pyrimidinyl, pyrazinyl, pyridazinyl, thienyl, furyl, quinolinyl, isoquinolinyl, dihydroisoquinolinyl, quinazolinyl, quinoxalinyl, indolyl, isoindolyl, benzimidazolyl, benzo[b]furyl, benzo[b]thienyl, phthalazinyl, benzthiazolyl or cinnolinyl.

Phenylalkyl is, for example, benzyl, 1-(phenyl)eth-1-yl or 1-(phenyl)eth-2-yl.

Heteroarylalkyl is, for example, pyridinylmethyl, pyrimidinylmethyl or 1-(pyridinyl)eth-2-yl.

The group $S(O)_2NR^7R^8$ is, for example, $S(O)_2NH_2$, $S(O)_2NH(C_{1-4}$ alkyl), $S(O)_2N(C_{1-4}$ alkyl$)_2$, $S(O)_2$(4-C(O)H-piperazin-1-yl) or $S(O)_2$(4-$C(O)CH_3$-piperazin-1-yl).

Phenyl(C_{1-2} alkyl)NH is, for example, benzylamino. Heteroaryl(C_{1-2} alkyl)NH is, for example, pyridinylCH_2NH, pyrimidinylCH_2NH or pyridinyl$CH(CH_3)NH$.

In one aspect the present invention provides a compound of formula (I) wherein R^1 is C_{3-7} cycloalkyl (substituted by 1 or 2 fluorine atoms and optionally further substituted by C_{1-4} alkyl). Cycloalkyl is especially cyclohexyl. R^1 is, for example, 4,4-difluorocyclohex-1-yl.

In another aspect R^1 is N-linked heterocyclyl (substituted by 1 or 2 fluorine atoms and optionally further substituted by C_{1-4} alkyl). N-Linked heterocyclyl is especially piperidin-1-yl or pyrrolidin-1-yl. R^1 is, for example, 4-fluoro-piperidin-1-yl or 3-fluoro-pyrrolidin-1-yl.

When R^2 is C_{3-6} alkyl it is, for example, a butyl group (such as iso-butyl) and when it is C_{3-6} cycloalkyl it is, for example, cyclopropyl or cyclohexyl.

In yet another aspect R^2 is phenyl or 6-membered heteroaryl optionally substituted in the ortho or meta position.

In a further aspect R^2 is phenyl or 6-membered heteroaryl optionally substituted by halogen or CF_3, wherein halogen is especially fluorine or chlorine. For example R^2 is 3-fluorophenyl, 3-chlorophenyl, 3-CF_3-phenyl, 4-fluorophenyl or 4-CF_3-phenyl.

In a further aspect R^{2a}, R^3, R^{3a} and R^4 are all hydrogen.

In still further aspect R^{4a} is hydrogen or methyl.

In another aspect R^5 is hydrogen, methyl or ethyl. In yet another aspect of the invention R^5 is ethyl.

In a further aspect R^5 is iso-propyl.

In a still further aspect R^5 is C_{3-4} alkenyl, C_{3-4} alkynyl, C_{3-7} cycloalkyl or C_{3-7} cycloalkyl(C_{1-4} alkyl). For example R^5 is allyl, propargyl, cyclopropyl or cyclopropylCH_2. In another aspect R^5 is cyclopropyl or, especially, allyl.

In yet another aspect of the invention R^6 is phenyl, heteroaryl, phenylNH, heteroarylNH, phenyl(C_{1-2})alkyl, heteroaryl(C_{1-2})alkyl, phenyl(C_{1-2} alkyl)NH or heteroaryl(C_{1-2} alkyl)NH; wherein the phenyl and heteroaryl rings of R^6 are substituted by one of: $S(O)_mC_{1-4}$ alkyl, $NHC(O)NH_2$, $C(O)(C_{1-4}$ alkyl), CHF_2, CH_2F, CH_2CF_3 or OCF_3, and optionally further substituted by one or more of halo, cyano, nitro, hydroxy, C_{1-4} alkyl, C_{1-4} alkoxy, $S(O)_mC_{1-4}$ alkyl, $S(O)_2NR^7R^8$, $NHS(O)_2(C_{1-4}$ alkyl), NH_2, $NH(C_{1-4}$ alkyl), $N(C_{1-4}$ alkyl)$_2$, $NHC(O)NH_2$, $C(O)NH_2$, $C(O)NH(C_{1-4}$ alkyl), $NHC(O)(C_{1-4}$ alkyl), CO_2H, $CO_2(C_{1-4}$ alkyl), $C(O)(C_{1-4}$ alkyl), CF_3, CHF_2, CH_2F, CH_2CF_3 or OCF_3; wherein m, R^7 and R^8 are hereinbefore defined.

In a still further aspect of the invention R^6 is phenyl, heteroaryl, phenylNH, heteroarylNH, phenyl(C_{1-2})alkyl, heteroaryl(C_{1-2})alkyl, phenyl(C_{1-2} alkyl)NH or heteroaryl(C_{1-2} alkyl)NH (preferably phenyl or phenylCH_2); wherein the phenyl and heteroaryl rings of R^6 are substituted by $S(O)_2C_{1-4}$ alkyl, and optionally further substituted by one or more of halo, cyano, nitro, hydroxy, C_{1-4} alkyl, C_{1-4} alkoxy, $S(O)_mC_{1-4}$ alkyl, $S(O)_2NR^7R^8$, $NHS(O)_2(C_{1-4}$ alkyl), NH_2, $NH(C_{1-4}$ alkyl), $N(C_{1-4}$ alkyl)$_2$, $NHC(O)NH_2$, $C(O)NH_2$, $C(O)NH(C_{1-4}$ alkyl), $NHC(O)(C_{1-4}$ alkyl), CO_2H, $CO_2(C_{1-4}$ alkyl), $C(O)(C_{1-4}$ alkyl), CF_3, CHF_2, CH_2F, CH_2CF_3 or OCF_3; wherein m, R^7 and R^8 are hereinbefore defined.

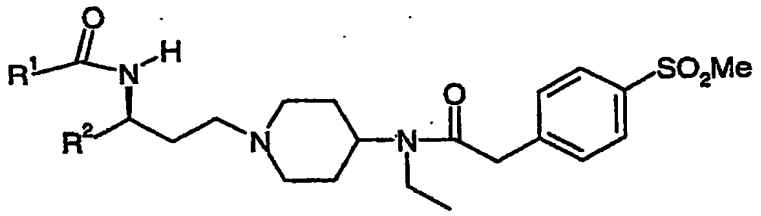
In another aspect of the invention R^6 is optionally substituted benzyl, especially benzyl singly substituted (such as in the 4-position) by $S(O)_2(C_{1-4})$alkyl (such as $S(O)_2CH_3$) or $S(O)_2NR^7R^8$ {R^7 and R^8 are, independently, hydrogen or C_{1-4} alkyl, or together with a nitrogen or oxygen atom, may join to form a 5- or 6-membered ring which is optionally substituted with C_{1-4} alkyl, C(O)H or $C(O)(C_{1-4}$ alkyl)} (such as $S(O)_2NH_2$, $S(O)_2NH(CH_3)$, $S(O)_2N(CH_3)_2$, $S(O)_2$(4-C(O)H-piperazin-1-yl) or $S(O)_2$(4-$C(O)CH_3$-piperazin-1-yl). The 5- or 6-membered ring is, for example, morpholine, thiomorpholine, piperidine, piperazine or pyrrolidine; but is especially piperazine.

In another aspect of the invention R^6 is benzyl singly substituted (such as in the 4-position) by $S(O)_2(C_{1-4})$alkyl (such as $S(O)_2CH_3$).

In a further aspect of the invention A is absent.

In another aspect of the invention A is CH_2CH_2.

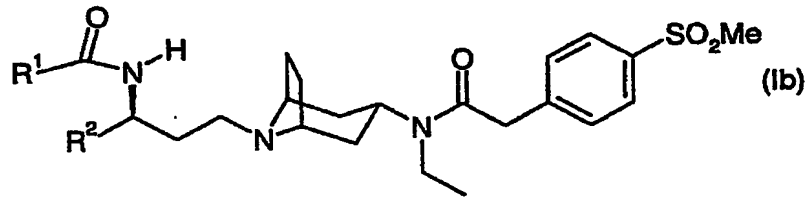
In yet another aspect the present invention provides a compound of formula (Ia):



(Ia)

wherein R^1 and R^2 are as defined above, and having the absolute configuration shown.

In a still further aspect the present invention provides a compound of formula (Ib):



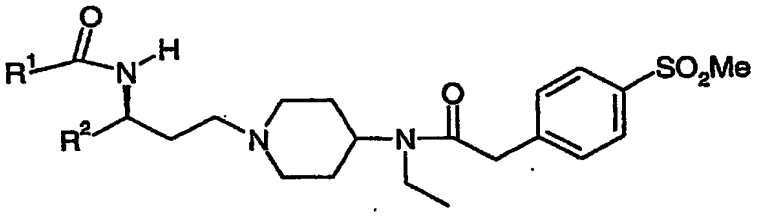
(Ib)

wherein R^1 and R^2 are as defined above, and having the absolute configuration shown.

The following compounds illustrate the invention.

TABLE I

Table I comprises compounds of formula (Ia).

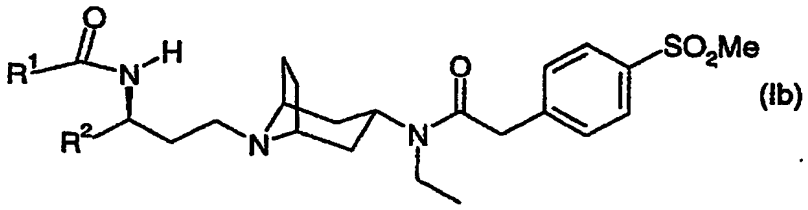


(Ia)

Compound No.	R^1	R^2	LCMS (MH+)
1	4,4-difluoro-cyclohexyl	Phenyl	604
2	4-fluoro-piperidin-1-yl	Phenyl	587
3	(*R*)-3-fluoro-pyrrolidin-1-yl	Phenyl	
4	(*S*)-3-fluoro-pyrrolidin-1-yl	Phenyl	

TABLE II

Table I comprises compounds of formula (Ib).

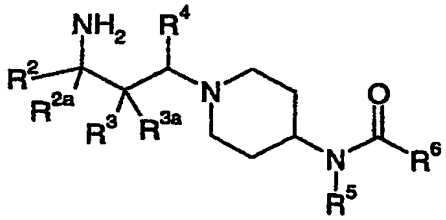


(Ib)

Compound No.	R^1	R^2	LCMS (MH+)
1	4,4-difluoro-cyclohexyl	Phenyl	604
2	4-fluoro-piperidin-1-yl	Phenyl	
3	(*R*)-3-fluoro-pyrrolidin-1-yl	Phenyl	
4	(*S*)-3-fluoro-pyrrolidin-1-yl	Phenyl	

The compounds of formulae (I), (Ia) and (Ib) can be prepared as described below, by adaptation of methods described in the art (such as WO 01/90106) or by following or adapting the Examples or Methods provided below.

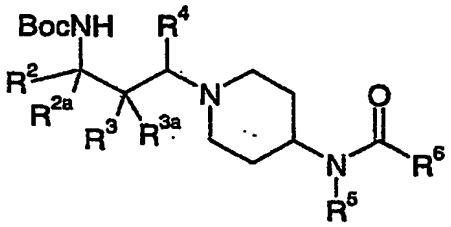
Specifically, a compound of formula (I) or (Ia) can be prepared by treating a compound of formula (II):



(II)

with: an acid chloride of formula $R^1C(O)Cl$, in the presence of a base (such as a tertiary amine, for example triethylamine) and in a suitable solvent (such as a chlorinated hydrocarbon, for example dichloromethane); or an acid of formula R^1CO_2H in the presence of a suitable coupling agent (such as O-(7-azabenzotriazol-1-yl)-*N*,*N*,*N*',*N*'-tetramethyluronium hexafluorophosphate [HATU] or bromo-tris-pyrrolidino-phosphonium hexafluorophosphate [PyBrop]) in the presence of a suitable base (such as a tertiary amine, for example diisopropylethylamine) in a suitable solvent (such as *N*-methylpyrrolidinone).

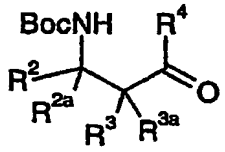
A compound of formula (II) can be prepared by treating a compound of formula (III):



(III)

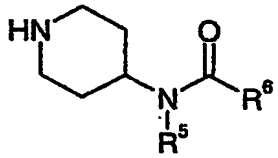
with trifluoroacetic acid or hydrochloric acid in the presence of methanol, and then basifying to release the free amine form of formula (II).

A compound of formula (III) can be prepared by reductively aminating a compound of formula (IV):



(IV)

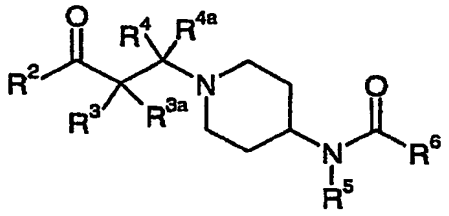
with a compound of formula (V):



(V)

in the presence of a suitable solvent (such as an aliphatic alcohol such as methanol), a suitable organic acid (such as an aliphatic acid, for example acetic acid) and a suitable reducing agent (such as sodium triacetoxyborohydride or sodium cyanoborohydride).

A compound of formula (II) wherein R^{2a} is hydrogen can be prepared by reductive amination of a compound of formula (VI):



(VI)

for example by reacting a compound of formula (VI) with hydroxylamine and hydrogenating the product so formed with hydrogen in the presence of a suitable metal catalyst (such as palladium or platinum catalyst, for example palladium on charcoal).

A compound of formula (VI), wherein R^{4a} is hydrogen, can be prepared by reacting a compound of formula (V) with:

- an alkyl halide of formula $R^2C(O)CR^3R^{3a}CHR^4X$ (wherein X is halogen, such as chloro, bromo or iodo) in the presence of a suitable base (such as potassium carbonate) and a suitable solvent (such as acetone); or,
- compounds of formula $R^2C(O)CHR^3R^{3a}$ and R^4CHO in the presence of a suitable acid (such as acetic acid).

A compound of formula (VI), wherein R^{3a} is hydrogen, can be prepared by reacting a compound of formula (V) with an alkene of formula $R^2C(O)CR^3=CR^4R^{4a}$ in a suitable solvent (such as an aliphatic alcohol, for example ethanol) at a temperature in the range -10 to 100°C.

The starting materials for these processes are commercially available, can be prepared by literature methods or can be prepared by adapting literature methods. In a further aspect the invention provides processes for preparing the compounds of formulae (I) and (Ia). Many of the intermediates in the processes are novel and these are provided as further features of the invention.

Compounds of formula (Ib) can be prepared by referring to WO 01/90106 and WO 01/87839.

The compounds of the invention have activity as pharmaceuticals, in particular as modulators (such as agonists, partial agonists, inverse agonists or antagonists) of chemokine receptor (especially CCR5) activity, and may be used in the treatment of autoimmune, inflammatory, proliferative or hyperproliferative diseases, or immunologically-mediated diseases (including rejection of transplanted organs or tissues and Acquired Immunodeficiency Syndrome (AIDS)). Examples of these conditions are:

(1) (the respiratory tract) obstructive diseases of airways including: chronic obstructive pulmonary disease (COPD) (such as irreversible COPD); pulmonary fibrosis; asthma {such as bronchial, allergic, intrinsic, extrinsic or dust asthma, particularly chronic or inveterate asthma (for example late asthma or airways hyper-responsiveness)}; bronchitis {such as eosinophilic bronchitis}; acute, allergic, atrophic rhinitis or chronic rhinitis including rhinitis caseosa, hypertrophic rhinitis, rhinitis purulenta, rhinitis sicca or rhinitis medicamentosa; membranous rhinitis including croupous, fibrinous or pseudomembranous rhinitis or scrofoulous rhinitis; seasonal rhinitis including rhinitis nervosa (hay fever) or vasomotor rhinitis; sarcoidosis; farmer's lung and related diseases; nasal polyposis; fibroid lung or idiopathic interstitial pneumonia;

(2) (bone and joints) arthrides including rheumatic, infectious, autoimmune, seronegative spondyloarthropathies (such as ankylosing spondylitis, psoriatic arthritis or Reiter's disease), Behcet's disease, Sjogren's syndrome or systemic sclerosis;

(3) (skin and eyes) psoriasis, atopic dermatitis, contact dermatitis or other eczmatous dermitides, seborrhoetic dermatitis, lichen planus, phemphigus, bullous phemphigus, epidermolysis bullosa, urticaria, angiodermas, vasculitides erythemas, cutaneous eosinophilias, uveitis, alopecia areata or vernal conjunctivitis;

(4) (gastrointestinal tract) Coeliac disease, proctitis, eosinophilic gastro-enteritis, mastocytosis, Crohn's disease, ulcerative colitis, irritable bowel disease or food-related allergies which have effects remote from the gut (for example migraine, rhinitis or eczema);

(5) (Allograft rejection) acute and chronic following, for example, transplantation of kidney, heart, liver, lung, bone marrow, skin or cornea; or chronic graft versus host disease; and/or

(6) (other tissues or diseases) Alzheimer's disease, multiple sclerosis, atherosclerosis, inhibiting the entry of viruses into target cells, Acquired Immunodeficiency Syndrome (AIDS), lupus disorders (such as lupus erythematosus or systemic lupus), erythematosus, Hashimoto's thyroiditis, myasthenia gravis, type I diabetes, nephrotic syndrome, eosinophilia fascitis, hyper IgE syndrome, leprosy (such as lepromatous leprosy), Peridontal disease, sezary syndrome, idiopathic thrombocytopenia pupura, disorders of the menstrual cycle, glomerulonephritis or cerebral malaria.

The compounds of the present invention are also of value in inhibiting the entry of viruses (such as human immunodeficiency virus (HIV)) into target calls and, therefore, are of value in the prevention of infection by viruses (such as HIV), the treatment of infection by viruses (such as HIV) and the prevention and/or treatment of acquired immune deficiency syndrome (AIDS).

According to a further feature of the invention there is provided a compound of the formula (I), (Ia) or (Ib), or a pharmaceutically acceptable salt thereof or a solvate thereof, for use in a method of treatment of a warm blooded animal (such as man) by therapy (including prophylaxis).

According to a further feature of the present invention there is provided a method for modulating chemokine receptor activity (especially CCR5 receptor activity) in a warm blooded animal, such as man, in need of such treatment, which comprises administering to

said animal an effective amount of a compound of the present invention, or a pharmaceutically acceptable salt thereof or a solvate thereof.

The present invention further provides a method of treating a chemokine mediated disease state (especially a CCR5 mediated disease state, such as rheumatoid arthritis) in a warm blooded animal (such as man) suffering from, or at risk of, said disease, which comprises administering to an animal in need of such treatment a therapeutically effective amount of a compound of formula (I), (Ia) or (Ib), or a pharmaceutically acceptable salt thereof or solvate thereof.

The invention also provides a compound of the formula (I), (Ia) or (Ib), or a pharmaceutically acceptable salt thereof or a solvate thereof, for use in therapy (including prophylaxis); for example in the treatment of a chemokine mediated disease state (especially a CCR5 mediated disease state) in a warm blooded animal, such as man, such as in the treatment of rheumatoid arthritis.

The invention also provides a compound of the formula (I), (Ia) or (Ib), or a pharmaceutically acceptable salt thereof or a solvate thereof, for use as a medicament, especially a medicament for the treatment of rheumatoid arthritis.

In another aspect the present invention provides the use of a compound of the formula (I), (Ia) or (Ib), or a pharmaceutically acceptable salt thereof or a solvate thereof, in the manufacture of a medicament for use in therapy (for example in modulating chemokine receptor activity (especially CCR5 receptor activity (especially in the treatment of rheumatoid arthritis)) in a warm blooded animal, such as man).

The invention further provides the use of a compound of formula (I), (Ia) or (Ib), or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for use in the treatment of:

(1) (the respiratory tract) obstructive diseases of airways including: chronic obstructive pulmonary disease (COPD) (such as irreversible COPD); asthma {such as bronchial, allergic, intrinsic, extrinsic or dust asthma, particularly chronic or inveterate asthma (for example late asthma or airways hyper-responsiveness)}; bronchitis {such as eosinophilic bronchitis}; acute, allergic, atrophic rhinitis or chronic rhinitis including rhinitis caseosa, hypertrophic rhinitis, rhinitis purulenta, rhinitis sicca or rhinitis medicamentosa; membranous rhinitis including croupous, fibrinous or pseudomembranous rhinitis or scrofoulous rhinitis; seasonal rhinitis including rhinitis nervosa (hay fever) or vasomotor rhinitis; sarcoidosis; farmer's lung and related diseases; nasal polyposis; fibroid lung or idiopathic interstitial pneumonia;

(2) (bone and joints) arthrides including rheumatic, infectious, autoimmune, seronegative spondyloarthropathies (such as ankylosing spondylitis, psoriatic arthritis or Reiter's disease), Behcet's disease, Sjögren's syndrome or systemic sclerosis;

(3) (skin and eyes) psoriasis, atopic dermatitis, contact dermatitis or other eczmatous dermitides, seborrhoetic dermatitis, lichen planus, phemphigus, bullous phemphigus, epidermolysis bullosa, urticaria, angiodermas, vasculitides erythemas, cutaneous eosinophilias, uveitis, alopecia areata or vernal conjunctivitis;

(4) (gastrointestinal tract) Coeliac disease, proctitis, eosinophilic gastro-enteritis, mastocytosis, Crohn's disease, ulcerative colitis, irritable bowel disease or food-related allergies which have effects remote from the gut (for example migraine, rhinitis or eczema);

(5) (Allograft rejection) acute and chronic following, for example, transplantation of kidney, heart, liver, lung, bone marrow, skin or cornea; or chronic graft versus host disease; and/or

(6) (other tissues or diseases) Alzheimer's disease, multiple sclerosis, atherosclerosis, Acquired Immunodeficiency Syndrome (AIDS), lupus disorders (such as lupus erythematosus or systemic lupus), erythematosus, Hashimoto's thyroiditis, myasthenia gravis, type I diabetes, nephrotic syndrome, eosinophilia fascitis, hyper IgE syndrome, leprosy (such as lepromatous leprosy), Peridontal disease, sezary syndrome, idiopathic thrombocytopenia pupura or disorders of the menstrual cycle;

in a warm blooded animal, such as man.

In order to use a compound of the invention, or a pharmaceutically acceptable salt thereof or solvate thereof, for the therapeutic treatment of a warm blooded animal, such as man, in particular modulating chemokine receptor (for example CCR5 receptor) activity, said ingredient is normally formulated in accordance with standard pharmaceutical practice as a pharmaceutical composition.

Therefore in another aspect the present invention provides a pharmaceutical composition which comprises a compound of the formula (I), (Ia) or (Ib), or a pharmaceutically acceptable salt thereof or a solvate thereof (active ingredient), and a pharmaceutically acceptable adjuvant, diluent or carrier. In a further aspect the present invention provides a process for the preparation of said composition which comprises mixing active ingredient with a pharmaceutically acceptable adjuvant, diluent or carrier. Depending on the mode of administration, the pharmaceutical composition will preferably comprise from 0.05 to 99 %w (per cent by weight), more preferably from 0.05 to 80 %w, still more

preferably from 0.10 to 70 %w, and even more preferably from 0.10 to 50 %w, of active ingredient, all percentages by weight being based on total composition.

The pharmaceutical compositions of this invention may be administered in standard manner for the disease condition that it is desired to treat. A suitable pharmaceutical composition of this invention is one suitable for oral administration in unit dosage form, for example a tablet or capsule which contains between 0.1mg and 1g of active ingredient.

Each patient may receive, for example, an intravenous, subcutaneous or intramuscular dose of 0.01mgkg^{-1} to 100mgkg^{-1} of the compound, preferably in the range of 0.1mgkg^{-1} to 20mgkg^{-1} of this invention, the composition being administered 1 to 4 times per day. The intravenous, subcutaneous and intramuscular dose may be given by means of a bolus injection. Alternatively the intravenous dose may be given by continuous infusion over a period of time. Alternatively each patient will receive a daily oral dose which is approximately equivalent to the daily parenteral dose, the composition being administered 1 to 4 times per day.

The invention will now be illustrated by the following non-limiting Examples in which, unless stated otherwise:

(i) temperatures are given in degrees Celsius (°C); operations were carried out at room or ambient temperature, that is, at a temperature in the range of 18-25°C;

(ii) organic solutions were dried over anhydrous magnesium sulphate; evaporation of solvent was carried out using a rotary evaporator under reduced pressure (600-4000 Pascals; 4.5-30 mm Hg) with a bath temperature of up to 60°C;

(iii) chromatography unless otherwise stated means flash chromatography on silica gel; thin layer chromatography (TLC) was carried out on silica gel plates; where a "Bond Elut" column is referred to, this means a column containing 10g or 20g of silica of 40 micron particle size, the silica being contained in a 60ml disposable syringe and supported by a porous disc, obtained from Varian, Harbor City, California, USA under the name "Mega Bond Elut SI". Where an "Isolute™ SCX column" is referred to, this means a column containing benzenesulphonic acid (non-endcapped) obtained from International Sorbent Technology Ltd., 1st House, Duffryn Industial Estate, Ystrad Mynach, Hengoed, Mid Glamorgan, UK. Where "Argonaut™ PS-*tris*-amine scavenger resin" is referred to, this means a *tris*-(2-aminoethyl)amine polystyrene resin obtained from Argonaut Technologies Inc., 887 Industrial Road, Suite G, San Carlos, California, USA.

(iv) in general, the course of reactions was followed by TLC and reaction times are given for illustration only;

(v) yields, when given, are for illustration only and are not necessarily those which can be obtained by diligent process development; preparations were repeated if more material was required;

(vi) when given, ^{1}H NMR data is quoted and is in the form of delta values for major diagnostic protons, given in parts per million (ppm) relative to tetramethylsilane (TMS) as an internal standard, determined at 300 MHz using perdeuterio DMSO (CD_3SOCD_3) as the solvent unless otherwise stated; coupling constants (J) are given in Hz;

(vii) chemical symbols have their usual meanings; SI units and symbols are used;

(viii) solvent ratios are given in percentage by volume;

(ix) mass spectra (MS) were run with an electron energy of 70 electron volts in the chemical ionisation (APCI) mode using a direct exposure probe; where indicated ionisation was effected by electrospray (ES); where values for m/z are given, generally only ions which indicate the parent mass are reported, and unless otherwise stated the mass ion quoted is the positive mass ion - $(M+H)^+$;

(x) LCMS characterisation was performed using a pair of Gilson 306 pumps with Gilson 233 XL sampler and Waters ZMD4000 mass spectrometer. The LC comprised water symmetry 4.6x50 column C18 with 5 micron particle size. The eluents were: A, water with 0.05% formic acid and B, acetonitrile with 0.05% formic acid. The eluent gradient went from 95% A to 95% B in 6 minutes. Where indicated ionisation was effected by electrospray (ES); where values for m/z are given, generally only ions which indicate the parent mass are reported, and unless otherwise stated the mass ion quoted is the positive mass ion - $(M+H)^+$ and

(xi) the following abbreviations are used:

THF	tetrahydrofuran;
Boc	tert-butoxycarbonyl
DCM	dichloromethane; and
HATU	O-(7-Azabenzotriazol-1-yl)-*N*,*N*,*N*',*N*'-tetramethyluronium hexafluorophosphate.

EXAMPLE 1

This Example illustrates the preparation of (*S*)-*N*-[1-(3-phenyl-3-[4,4-difluorocyclohexylcarboxyamino]propyl)-4-piperidinyl]-*N*-ethyl-4-methanesulfonylphenylacetamide (Compound No. 1 of Table I).

(*S*)-*N*-[1-(3-Phenyl-3-aminopropyl)-4-piperidinyl]-*N*-ethyl-4-methanesulfonylphenylacetamide dihydrochloride (Method A, 250mg), 4,4-difluorocyclohexane carboxylic acid (100mg) and *N,N*-di-isopropylethylamine (0.7mL) were stirred in DCM (5mL) at room temperature. To this solution was added HATU (200mg) and stirring was continued for 16 hours. 2N Sodium hydroxide solution (2mL) was added and the organic layer separated, washed with water and concentrated; the residue was purified by silica gel chromatography (eluent 0-30% methanol in ethyl acetate) to give the title compound as a colourless gum (110mg); NMR: 1.0 and 1.1 (t, 3H), 1.7 (m, 7H), 2.2 (m, 6H), 3.0 (m, 3H), 3.2 (s, 3H), 3.4 (q, 2H), 3.8 and 3.9 (s, 2H), 4.1 and 4.3 (m, 1H), 4.8 (m, 1H), 7.2 (m, 1H), 7.3 (m, 4H), 7.5 (d, 2H), 7.8 (d, 2H), 8.85 (m, 1H); MS: 604 (MH+).

EXAMPLE 2

This Example illustrates the preparation of (*S*)-*N*-[1-(3-phenyl-3-[4-fluoropiperidin-1-ylcarboxyamino]propyl)-4-piperidinyl]-*N*-ethyl-4-methanesulfonylphenylacetamide (Compound No. 2 of Table I).

To (*S*)-*N*-[1-(3-phenyl-3-[4-nitrophenoxycarboxyamino]propyl)-4-piperidinyl]-*N*-ethyl-4-methanesulfonylphenylacetamide (Method C, 150mg) in DCM (10mL) was added 4-fluoropiperidine hydrochloride (100mg) and *N,N*-di-isopropylethylamine (1mL). The resulting mixture was stirred at room temperature for 16 hours. 2N Sodium hydroxide solution (10mL) was added and the organic layer separated, washed with water, dried ($MgSO_4$) and concentrated; the residue was purified by silica gel chromatography (eluent 0-20% methanol in ethyl acetate) to give the title compound as a colourless gum (140mg); MS: 587 (MH+).

EXAMPLE 3

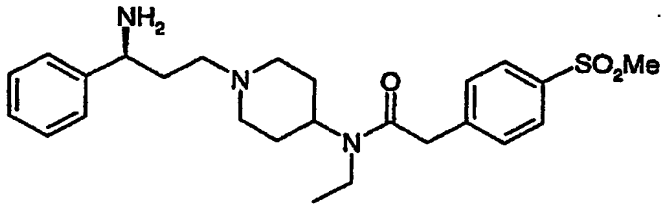
This Example illustrates the preparation of (*S*)-4,4-difluoro-cyclohexanecarboxylic acid [3-(3-{ethyl-[2-(4-methanesulfonyl-phenyl)-acetyl]-amino}-8-aza-bicyclo[3.2.1]oct-8-yl-exo)-1-phenyl-propyl]-amide (Compound No. 1 of Table II).

To a solution of *N*-(8-aza-bicyclo[3.2.1]oct-3-yl-exo)-*N*-ethyl-2-(4-methanesulfonyl-phenyl)-acetamide (Method D; 98mg, 0.28mmol) in DCM was added (*S*)-3-

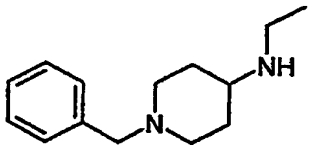
phenyl-3-(4,4-difluorocyclohexylcarbonylamino)propanal (Method E; 165mg, 0.56mmol). To the resulting mixture was added sodium triacetoxyborohydride (119mg). This was then stirred at room temperature for 18 h, washed with water, dried over $MgSO_4$ and concentrated. Purification was achieved by BondElut chromatography eluting with a gradient of DCM to 10% methanol and 1% 0.88 ammonia in DCM to give the title compound (143mg); NMR ($CDCl_3$): 1.1 and 1.2 (t, 3H), 1.3 (m, 1H), 1.9 (m, 19H), 2.3 (m, 1H), 2.5 (m, 1H), 3.0 (s, 3H), 3.3 (m, 4H), 3.8 (m, 2H), 3.6 and 4.4 (m, 1H), 5.0 (m, 1H), 7.2 (m, 5H), 7.4 (m, 2H), 7.9 (m, 2H); MS: 630 (MH+).

Method A

(S)-N-[1-(3-Phenyl-3-aminopropyl)-4-piperidinyl]-*N*-ethyl-4-methanesulfonylphenylacetamide dihydrochloride

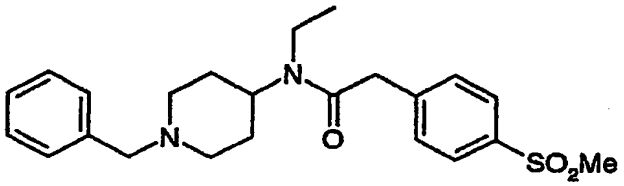


Step 1: Preparation of 1-phenylmethyl-4-ethylaminopiperidine dihydrochloride



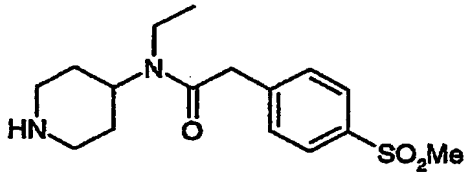
To a solution of 1-phenylmethyl-4-piperidone (25.0 g, 132 mmol) in THF (250 mL) was added ethylamine hydrochloride (12.0 g, 147 mmol) and methanol (50 mL) and the resulting mixture stirred at room temperature for 10 min. Sodium triacetoxyborohydride (40 g, 189 mmol) was added portionwise and the resulting mixture stirred at room temperature for 1 h. 2M Sodium hydroxide solution (250 mL) was added and the resulting mixture extracted with diethyl ether. The organic extracts were dried (K_2CO_3) and evaporated to give 1-phenylmethyl-4-ethylaminopiperidine as an oil. This was dissolved in ethanol (500 mL) and concentrated hydrochloric acid (20 mL) was added. The resulting crystals were collected, washed with diethyl ether and dried giving the sub-titled compound as a solid (38 g); NMR: ($CDCl_3$): 1.10 (t, 3H), 1.40 (m, 2H), 1.83 (m, 2H), 2.02 (m, 2H), 2.65 (q, 2H), 2.85 (m, 2H), 3.50 (s, 2H), 3.75 (m, 1H), 7.2 - 7.4 (m, 5H); MS: 219 (MH+).

Step 2: Preparation of *N*-(1-Phenylmethyl-4-piperidinyl)-*N*-ethyl-4-methanesulfonylphenylacetamide



To a solution of 1-phenylmethyl-4-ethylaminopiperidine dihydrochloride (32.0g, 110mmol) in DCM (500mL) was added *N,N*-diisopropylethylamine (60mL) with stirring to ensure complete dissolution. 4-Methanesulfonylphenylacetic acid (25.0g, 117mmol), 4-Dimethylaminopyridine (4-DMAP) (2.0g) and dicyclohexylcarbodiimide (DCCI) (25.0g, 121 mmol) were added and the resulting mixture was stirred at room temperature for 20 h. The precipitate was removed by filtration and the resulting solution was washed successively with 2N aqueous HCl, water and 1N aqueous NaOH, dried ($MgSO_4$) and evaporated. The residue was purified by silica gel chromatography (eluent 10% MeOH/ethyl acetate) to afford the sub-titled compound (35 g, 76%); NMR: 1.00 and 1.14 (t, 3H), 1.45 and 1.70 (m, 2H), 1.95 (br m, 2H), 2.80 (br m, 2H), 3.18 (s, 3H), 3.20 and 3.33 (q, 2H), 3.45 (s, 2H), 3.80 and 3.87 (s, 2H), 3.70 and 4.10 (m, 1H), 7.2 - 7.3 (m, 5H), 7.48 (m, 2H), 7.82 (m, 2H); MS: 415 (MH+).

Step 3: Preparation of *N*-(4-Piperidinyl)-*N*-ethyl-4-methanesulfonylphenylacetamide



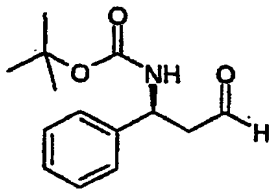
To a solution of *N*-(1-phenylmethyl-4-piperidinyl)-*N*-ethyl-4-methanesulfonylphenyl-acetamide (34g, 82mmol) in ethanol (600mL) was added ammonium formate (40g). The mixture was purged with argon and 30% Pd on carbon (4.2g) was added. The resulting mixture was stirred at reflux for 4 h, then allowed to cool and filtered through diatomaceous earth. The filtrate was evaporated to give a thick oil which solidified on standing to yield the sub-titled compound (24.9 g, 94%); NMR: 1.02 and 1.15 (t, 3H), 1.4 -1.6 (br m, 4H), 2.45 (m, 2H), 2.93 (br m, 2H), 3.18 (s, 3H), 3.20 and 3.32 (q, 2H), 3.72 and 4.18 (m, 1H), 3.80 and 3.87 (s, 2H), 7.50 (m, 2H), 7.85 (m, 2H); MS: 325 (MH+).

Step 4: Preparation of title compound

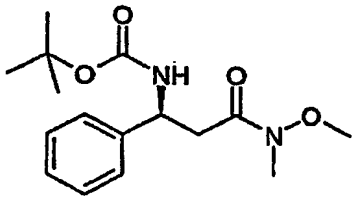
To a solution of (*S*)-3-phenyl-3-Bocaminopropanal (Method B, 1.4g, 5.6mmol) in ethanol (100mL) and DCM (50mL) was added *N*-(4-piperidinyl)-*N*-ethyl-4-methanesulfonylphenylacetamide (2.0g, 6.2mmol), glacial acetic acid (0.6mL, 10mmol) and sodium triacetoxyborohydride (2.0g, 9.4mmol) and the resulting mixture was stirred at room temperature for 18 h. The mixture was partitioned between DCM and 2M aqueous sodium hydroxide (35mL), and the organic phase was washed with water, dried and concentrated. The residue was suspended in methanol (10mL) and concentrated hydrochloric acid (10mL) was added. The resulting mixture was stirred for 30 min. then evaporated. The residue was azeotroped with ethanol and toluene and triturated with diethyl ether yielding the title compound as a solid (1.3g); NMR (d6 DMSO at 373K): 1.1 (t, 3H), 1.5 (m, 2H), 1.9 (m, 2H), 2.0 (m, 1H), 2.3 (m, 2H), 3.0 (m, 1H), 3.2 (m, 4H), 3.3 (q, 2H), 3.9 (s, 2H), 4.0 (m, 1H), 4.4 (m, 1H), 7.4 (m, 3H), 7.5 (m, 4H), 7.9 (m, 2H); MS: 458.

Method B

(*S*)-3-Phenyl-3-Boc-aminopropanal



Step 1: Preparation of (*S*)-*N*-Methyl-*N*-methoxy-3-phenyl-3-Bocaminopropionamide



To a solution of (*S*)-3-phenyl-3-Bocaminopropanoic acid (available from PepTech Corp. of Cambridge, Massachusetts, USA; 4.97g, 18.7mmol) in DCM (100mL) was added DIPEA (14.8mL, 84.8mmol) and *N*,*O*-dimethylhydroxylamine hydrochloride (2.21g, 22.7mmol) followed by HATU (8.44g, 84.8mmol). The resulting mixture was stirred at room temperature for 18h, diluted with DCM, washed with 2M aqueous sodium hydroxide and water. The organic phase was dried (Na_2SO_4) and concentrated. The residue was purified by

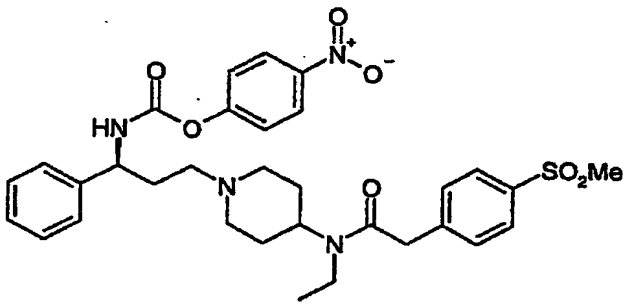
silica column chromatography (eluting with isohexane then 3:1 ethyl acetate to isohexane) giving the sub-titled compound as a colourless oil (5.58g, 97%); NMR ($CDCl_3$): 1.40 (s, 9H), 2.83 (dd, 1H), 3.01 (m, 1H), 3.08 (s, 3H), 3.52 (s, 3H), 5.10 (m, 1H), 7.28 (m, 5H); MS: 309.

Step 2: Preparation of title compound

To a solution of *(S)*-*N*-methyl-*N*-methoxy-3-phenyl-3-Bocaminopropionamide (17.9mmol) in toluene (180mL) at -20°C was added sodium bis(2-methoxyethoxy)aluminium hydride (65% solution in toluene, 35.8mmol) dropwise. The resulting mixture was stirred at -15°C for 1h. The mixture was washed with saturated aqueous sodium dihydrogen phosphate solution (250mL). The organic phase was dried (Na_2SO_4) and concentrated to give the title compound (5g); NMR: 1.4 (s, 9H), 2.8 (m, 2H), 5.1 (m, 1H), 7.3 (m, 5H), 8.6 (m, 1H), 9.6 (t, 1H).

Method C

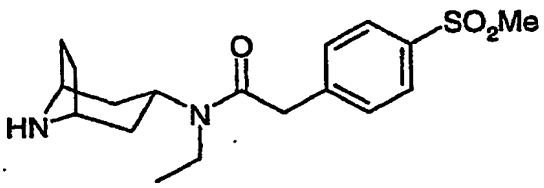
(S)-*N*-[1-(3-phenyl-3-[4-nitrophenoxycarboxyamino]propyl)-4-piperidinyl]-*N*-ethyl-4-methanesulfonylphenylacetamide



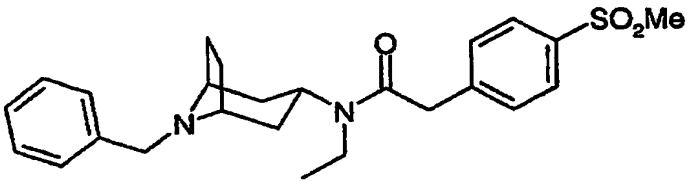
To *(S)*-*N*-[1-(3-phenyl-3-aminopropyl)-4-piperidinyl]-*N*-ethyl-4-methanesulfonylphenylacetamide dihydrochloride (2.0g, 3.8mmol) in DCM (50mL) was added *N,N*-di-isopropylethylamine (2mL) and 4-nitrophenyl chloroformate (1.0g, 4.9mmol) and the resulting mixture stirred at ambient temperature for 16 hours. The mixture was washed with saturated sodium bicarbonate solution (50mL) and dried over anhydrous magnesium sulphate. The residue was purified by silica gel chromatography (eluent 0-10% methanol in ethyl acetate) to give the title compound as a pale yellow gum (2g).

Method D

N-(8-Aza-bicyclo[3.2.1]oct-3-yl-exo)-*N*-ethyl-2-(4-methanesulfonyl-phenyl)-acetamide



Step 1: Preparation of *N*-(8-Benzyl-8-aza-bicyclo[3.2.1]oct-3-yl)-*N*-ethyl-2-(4-methanesulfonyl-phenyl)-acetamide



To a solution of 8-Benzyl-8-aza-bicyclo[3.2.1]oct-3-yl-exo-amine† (2.81g, 13 mmol) in DCM (40mL) was added acetaldehyde (0.69g, 16mmol) and the resulting mixture stirred at room temperature for 1h. Sodium triacetoxyborohydride (3.3 g, 16mmol) was added portionwise and the resulting mixture stirred at room temperature for 16h. The mixture was then washed with water, dried over $MgSO_4$ and concentrated. This material was then dissolved in DCM (50mL) and 4-methanesulfonylphenylacetic acid (3.1g, 14mmol) and diisopropylcarbodiimide (2.1g, 14mmol) were added and the resulting mixture stirred for 2h. The precipitate was removed by filtration and the crude material was adsorbed onto silica. Silica gel chromatography (eluent: 100% DCM to 10% methanol and 1% 0.88 ammonia in DCM) gave the sub-titled compound as a foam (0.37g); NMR ($CDCl_3$): 1.2 and 1.3 (t, 3H), 1.4 (m, 1H), 1.5 (m, 1H), 1.7 (m, 2H), 1.9 (m, 2H), 2.0 (m, 2H), 3.0 (s, 3H), 3.3 (m, 4H), 3.5 (d, 2H), 3.8 (d, 2H), 3.9 and 4.8 (m, 1H), 7.3 (m, 5H), 7.5 (m, 2H), 7.9 (m, 2H); MS: 441 (MH+).

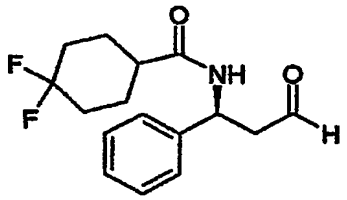
Step 2: Preparation of title compound

To a solution of *N*-(8-Benzyl-8-aza-bicyclo[3.2.1]oct-3-yl-exo)-*N*-ethyl-2-(4-methanesulfonyl-phenyl)-acetamide (0.37g, 0.85mmol) in ethanol (20mL) was added 20% palladium hydroxide on carbon (0.04g) and the resulting mixture was stirred under an atmosphere of hydrogen for 2 days. The catalyst was removed by filtration and the resulting solution was adsorbed onto silica. The residue was purified by silica gel chromatography (eluent: DCM to 10% methanol and 1% 0.88 ammonia in DCM) to afford the sub-titled compound as an oil(0.1g); NMR ($CDCl_3$): 1.1 and 1.2 (t, 3H), 1.3 (m, 1H), 1.4 (m, 2H), 1.7

(m, 5H), 2.1 (br s, 1H), 3.0 (s, 3H), 3.3 (m, 2H), 3.6 (m, 2H), 3.7 and 3.8 (s, 2H), 3.8 and 4.8 (m, 1H), 7.4 (m, 2H), 7.9 (m, 2H); MS: 351 (MH+).

Method E

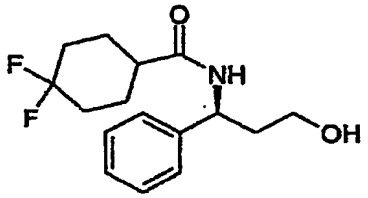
(*S*)-3-Phenyl-3-(4,4-difluorocyclohexylcarbonylamino)propanal



Step 1: Preparation of (*S*)-3-amino-3-phenyl-propionic acid methyl ester hydrochloride

To a solution of (*S*)-3-Bocamino-3-phenyl-propionic acid (5g, 18.8mmol) in methanol (50mL) was added thionyl chloride (1.5mL, 20.7mmol) dropwise. The resulting mixture was stirred at reflux for 4h then allowed to cool and concentrated. The residue was used directly in the next reaction.

Step 2: Preparation (*S*)-3-phenyl-3-(4,4-difluorocyclohexylcarbonylamino)propanol



To a solution of (*S*)-3-amino-3-phenyl-propionic acid methyl ester hydrochloride (3.31g, 15.3 mmol) in DCM (50mL) was added triethylamine (1.71g, 17mmol) and the resulting mixture stirred at 0°C for 10min. Then 4,4-difluorocyclohexane carboxylic acid (2.8g, 17mmol) and diisopropylcarbodiimide (2.5g, 17mmol) were added portionwise and the resulting mixture stirred at room temperature for 16h. The mixture was then washed with water, dried over $MgSO_4$ and concentrated. Silica gel chromatography (eluent: isohexane to diethyl ether) gave the sub-titled compound as a solid (3.7g). This material was then dissolved in THF under an atmosphere of argon and lithium aluminium hydride (11mL, 1M in THF) was added dropwise at 0°C. After stirring for 15min, the reaction was quenched with 2M NaOH and separated. The organic layer was dried over $MgSO_4$ purified by silica gel chromatography (eluent: isohexane to ethyl acetate) to afford the sub-titled compound as a

solid (1.32g); NMR ($CDCl_3$): 1.8 (m, 8H), 2.2 (m, 3H), 3.6 (m, 1H), 3.7 (m, 1H), 5.2 (m, 1H), 7.3 (m, 5H); MS: 297 (M+).

Step 3: Preparation of title compound

To a solution of (*S*)-3-phenyl-3-(4,4-difluorocyclohexylcarbonylamino)propanol (0.17g, 0.56mmol) in DCM (5mL) was added Dess Martin periodinane (0.26g, 0.62mmol) and the resulting mixture was stirred for 1h. The mixture was then washed with 2M NaOH, dried over $MgSO_4$ and concentrated. The resulting residue was then used directly in the preparation of Example 3.

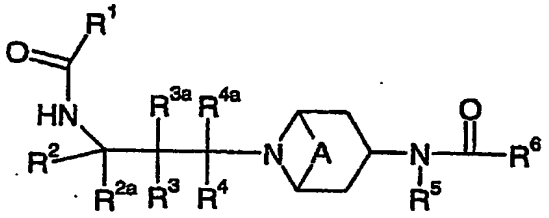
[†] John S. Kiely, Marland P. Hutt, Townley P. Culbertson, Ruth A. Bucsh and Donald F. Worth; J. Med. Chem., 1991, 34, 656.

EXAMPLE 4

The ability of compounds to inhibit the binding of RANTES or MIP-1α was assessed by an *in vitro* radioligand binding assay. Membranes were prepared from Chinese hamster ovary cells which expressed the recombinant human CCR5 receptor. These membranes were incubated with 0.1nM iodinated RANTES or MIP-1α, scintillation proximity beads and various concentrations of the compounds of the invention in 96-well plates. The amount of iodinated RANTES or MIP-1α bound to the receptor was determined by scintillation counting. Competition curves were obtained for compounds and the concentration of compound which displaced 50% of bound iodinated RANTES or MIP-1α was calculated (IC_{50}). Certain compounds of formula (I) had an IC_{50} of less than 50μM.

CLAIMS

1. A compound of formula (I):



(I)

wherein:

A is CH_2CH_2 or A is absent;

R^1 is C_{3-7} cycloalkyl (substituted by one or two fluorine atoms and optionally further substituted by C_{1-4} alkyl) or N-linked heterocyclyl (substituted by one or two fluorine atoms and optionally further substituted by C_{1-4} alkyl);

R^2 is C_{3-6} alkyl or C_{3-6} cycloalkyl, or phenyl or heteroaryl either of which is optionally substituted by halogen, C_{1-4} alkyl, C_{1-4} alkoxy, $S(O)_n(C_{1-4}$ alkyl), nitro, cyano or CF_3;

R^{2a}, R^4 and R^{4a} are, independently, hydrogen or C_{1-4} alkyl;

R^3 and R^{3a} are, independently, hydrogen or C_{1-4} alkyl or C_{1-4} alkoxy;

R^5 is hydrogen, C_{1-4} alkyl (optionally substituted by halogen, hydroxy, C_{1-4} alkoxy, C_{3-7} cycloalkyl, SH, C_{1-4} alkylthio, cyano or $S(O)_q(C_{1-4}$ alkyl)), C_{3-4} alkenyl, C_{3-4} alkynyl or C_{3-7} cycloalkyl;

R^6 is phenyl, heteroaryl, phenylNH, heteroarylNH, phenyl(C_{1-2})alkyl, heteroaryl(C_{1-2})alkyl, phenyl(C_{1-2} alkyl)NH or heteroaryl(C_{1-2} alkyl)NH;

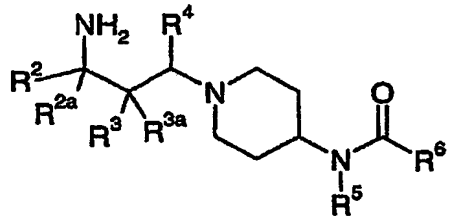
wherein the phenyl and heteroaryl rings of any of the foregoing are, unless stated otherwise, independently optionally substituted by halo, cyano, nitro, hydroxy, C_{1-4} alkyl, C_{1-4} alkoxy, $S(O)_mC_{1-4}$ alkyl, $S(O)_2NR^7R^8$, $NHS(O)_2(C_{1-4}$ alkyl), NH_2, $NH(C_{1-4}$ alkyl), $N(C_{1-4}$ alkyl)$_2$, $NHC(O)NH_2$, $C(O)NH_2$, $C(O)NH(C_{1-4}$ alkyl), $NHC(O)(C_{1-4}$ alkyl), CO_2H, $CO_2(C_{1-4}$ alkyl), $C(O)(C_{1-4}$ alkyl), CF_3, CHF_2, CH_2F, CH_2CF_3 or OCF_3;

R^7 and R^8 are, independently, hydrogen or C_{1-4} alkyl, or together with a nitrogen or oxygen atom, may join to form a 5- or 6-membered ring which is optionally substituted with C_{1-4} alkyl, C(O)H or $C(O)(C_{1-4}$ alkyl);

m, n and q are, independently, 0, 1 or 2;

or a pharmaceutically acceptable salt thereof or a solvate thereof.

2. A process for the preparation of a compound of formula (I) as claimed in claim 1, wherein A is absent, comprising treating a compound of formula (II):



(II)

with:

an acid chloride of formula $R^1C(O)Cl$, in the presence of a base and in a suitable solvent; or,

an acid of formula R^1CO_2H, in the presence of a suitable coupling agent, a suitable base and in a suitable solvent.

3. A pharmaceutical composition which comprises a compound of the formula (I), or a pharmaceutically acceptable salt thereof or solvate thereof as claimed in claim 1, and a pharmaceutically acceptable adjuvant, diluent or carrier.

4. A compound of the formula (I), or a pharmaceutically acceptable salt thereof or solvate thereof as claimed in claim 1, for use in therapy.

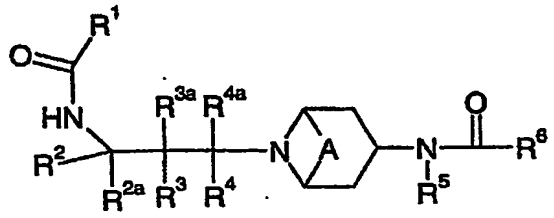
5. A compound of formula (I), or a pharmaceutically acceptable salt thereof or solvate thereof as claimed in claim 1, in the manufacture of a medicament for use in therapy.

6. A method of treating a chemokine mediated disease state in a warm blooded animal suffering from, or at risk of, said disease, which comprises administering to an animal in need of such treatment a therapeutically effective amount of a compound of formula (I), or a pharmaceutically acceptable salt thereof or solvate thereof as claimed in claim 1.

ABSTRACT

CHEMICAL COMPOUNDS

The invention provides a compound of formula (I):



(I)

wherein R^1, R^2, R^3, R^{3a}, R^4, R^{4a}, R^5, and R^6 are as defined; or a pharmaceutically acceptable salt thereof or a solvate thereof; compositions containing these compounds, processes for preparing them and their use as modulators of chemokine activity (especially CCR5 activity).